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IN THE UNITED STATES RECEIVING OFFICE (US/RO)

Applicant: Bruno Tocque et al.

Customer No: 21559

Serial No:

Filed: March 6, 2002

Titled: GENETIC MARKERS OF TOXICITY,  
PREPARATION AND USES

Box PCT  
Assistant Commissioner for Patents  
Washington, DC 20231

PRELIMINARY AMENDMENT

Prior to examination, kindly amend the above-referenced application as follows:

In the Specification

On page 1, after the title, insert the following paragraph:

--Cross Reference To Related Applications

This application is a continuation-in-part of U.S.S.N. 09/456,370, filed December 8, 1999. This application also claims priority from French application

42. The method according to claim 40, wherein the nucleic probes a) are cDNA or cDNA fragments prepared from RNAs of treated and untreated cells.

43. The method according to claim 40, wherein the nucleic probes a) are amplification products.

44. The method according to claim 40, wherein the nucleic probes a) are labeled by radioactive, fluorescent, enzymatic or colorimetric labels.

45. The method according to claim 40, wherein the test compound is an individual compound or is present in a mixture with other substances.

46. The method according to claim 40, wherein the library b) further comprises nucleic acid clones specific for genes whose level of expression is modified in a situation of apoptosis.

47. The method according to claim 40, wherein the library b) is prepared by (i) hybridizing a first nucleic acid population from a mammalian cell in a situation of apoptosis and a second nucleic acid population from a cell in a control situation and (ii) separating, from the hybrids formed, nucleic acids comprising an unpaired region.

serial no. 99/11405, filed September 13, 1999, and international application serial no. PCT/FR00/02503, filed on September 12, 2000.--

In the claims

Please cancel claims 1-39 and add the following new claims:

40. A method of analysis of the toxic potential of a test compound, said method comprising separately contacting, under conditions allowing hybridisation to occur,

a) labeled nucleic acid probes corresponding to RNA molecules from mammalian cells treated with said test compound on the one hand and from untreated mammalian cells on the other hand, with

b) a library of nucleic acids, wherein said library comprises, immobilized on a support, nucleic acid clones specific for splicing forms of genes, said splicing forms being characteristic of apoptosis,

the hybridization profile indicating the toxic potential of the test compound.

41. The method according to claim 40, wherein the nucleic probes a) correspond to messenger RNAs from treated and untreated cells.





(ii) labelled nucleic probes corresponding to mRNA molecules from mammalian cells treated with said test compound and said nucleic acid library, the hybridization profile indicating the toxic potential of the test compound.

57. The method according to claim 56, wherein the nucleic acid library comprises at least 1 clone of sequence selected from SEQ ID Nos: 1 to 37.

58. A kit for the study or assessment of the toxic potential of a test compound, said kit comprising a nucleic acid library comprising at least one nucleic acid clone specific for a gene selected from the following genes: Aldolase A; S4 subunit of proteasome 26S; Alpha-tubulin; Glucosidase II; lamin B receptor homologue; EF1-alpha; Fra-1; tyrosine kinase AX1 receptor; spliceosome Protein SAP62; TRAF-3; EF2; TEF-5; CDC25b; interleukine-1 receptor-associated kinase (« IRAK »); WAF-1; c-fos (exon 4); ckshs1; PL16; NFAR-2; phosphatidylinositol4-kinase, ERF, Eph type receptor tyrosine kinase (hEphB1b); BAF60b protein of the SWI/SNF complex; EB1; MSS1; retinoic acid alpha receptor (RARa); translation initiation factor eiF4A; STE20 type kinase; protein HSP 90kda; Lipocortin II; protein TPT1 (« translationally controlled tumor proteon ») Hsc70; Cytokeratin 18; 2-oxoglutarate dehydrogenase; mitochondrial gene NADH6; mitochondrial gene NADH deshydrogenase 4; alpha subunit of mitochondrial ATP synthase.



solid support of one or more nucleic acid libraries according to claim 61 or obtained by the process of claim 63.

65. A method for the identification of SNPs or other mutations or polymorphisms that allow the assessment of the response of a subject to a given compound, the method comprising (i) the identification *in vitro* of nucleic acids characteristic of splicing events induced in a cell treated with said compound and (ii) the identification of SNPs or other mutations or polymorphisms in the gene or genes corresponding to nucleic acids identified in (i), said SNPs or other mutations or polymorphisms allowing the assessment of the response of a subject to said given compound.

66. A method for the evaluation of the sensitivity or of the response of a subject to a test compound, comprising the analysis, from a biological sample comprising DNA from said subject, of the presence in the DNA of said subject of polymorphisms, SNPs, or other genomic alterations present in genes whose splicing is modified in response to said compound.



REMARKS

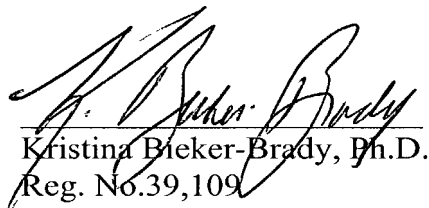
The specification was amended in order to incorporate the priority information into the text. Claims 1-39 were canceled and replaced with claims 40-66 in order to place them in the most appropriate form for the U.S. No new matter has been added by any of the above amendments.

If there are any charges or credits not covered, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

March 14, 2002

  
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